Interaction of the antifungal ketoconazole and its diphenylphosphine derivatives with lipid bilayers: Insights into their antifungal action

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Streszczenie

Ketoconazole (**Ke**) is an important antifungal drug, and two of its diphenylphosphinemethyl derivatives (**KeP**: Ph_2PCH_2-Ke and **KeOP**: $Ph_2P(O)CH_2$-Ke) have shown improved antifungal activity, namely against a yeast strain lacking ergosterol, suggesting alternative modes of action for azole compounds. In this context, the interactions of these compounds with a model of the cell membrane were investigated, using POPC (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) large unilamellar vesicles and taking advantage of the intrinsic fluorescence of **Ke**, **KeP** and **KeOP**. Steady-state fluorescence spectra and anisotropy, including partition and aggregation studies, as well as fluorescence lifetime measurements, were carried out. In addition, the ability of the compounds to increase membrane permeability was assessed through carboxyfluorescein leakage. The membrane/water mole fraction partition coefficients ($K_{p,x}$): (3.31 ± 0.36) $x10^5$, (8.31 ± 1.60) $x10^5$ and (4.66 ± 0.72) $x10^6$, for **Ke**, **KeP** and **KeOP**, respectively, show that all three compounds have moderate to high affinity for the lipid bilayer. Moreover, **KeP**, and particularly **KeOP** interact more efficiently with POPC bilayers than **Ke**, which correlates well with their *in vitro* antifungal activity. Furthermore, although the three compounds disturb the lipid bilayer, **KeOP** is the quickest and most efficient one. Hence, the higher affinity and ability to permeabilize the membrane of **KeOP** when compared to that of **KeP**, despite the higher lipophilicity of the latter, points to an important role of $Ph_2P(O)CH_2$- oxygen. Overall, this work suggests that membrane interactions are important for the antifungal activity of these azoles and should be considered in the design of new therapeutic agents.

Słowa kluczowe

Ketoconazole, Drug-membrane interaction, Antifungal agents, Fluorescence spectroscopy, Diphenylphosphinomethyl derivatives, Phospholipid bilayer

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